Answer 1:

Bibliographic Information

The mismatch repair protein, hMLH1, mediates 5-substituted halogenated thymidine analogue cytotoxicity, DNA incorporation, and radiosensitization in human colon cancer cells. Berry, Suzanne E.; Garces, Christopher; Hwang, Hwa-Shin; Kunugi, Keith; Meyers, Mark; Davis, Thomas W.; Boothman, David A.; Kinsella, Timothy J. Department of Radiation Oncology, School of Medicine and University Hospitals of Cleveland/Ireland Cancer Center, Case Western Reserve University, Cleveland, OH, USA. Cancer Research (1999), 59(8), 1840-1845. Publisher: AACR Subscription Office, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 131:55871 AN 1999:273035 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Deficiency in DNA mismatch repair (MMR) is found in some hereditary (hereditary nonpolyposis colorectal cancer) and sporadic colon cancers as well as other common solid cancers. MMR deficiency has recently been shown to impart cellular resistance to multiple chem. agents, many of which are commonly used in cancer chemotherapy. It is therefore of interest to find an approach that selectively targets cells that have lost the ability to perform MMR. In this study, we examine the response of MMR-proficient (hMLH1+) and MMR-deficient (hMLH1-) colon carcinoma cell lines to the halogenated thymidine (dThd) analogs iododeoxyuridine (IdUrd) and bromodeoxyuridine (BrdUrd) before and after irradn. These dThd analogs are used clin. as exptl. sensitizing agents in radioresistant human cancers, and there is a direct correlation between the levels of dThd analog DNA incorporation and tumor radiosensitization. In contrast to the well-characterized, marked increase in cytotoxicity (>1 log cell kill) found with 6-thioguanine exposures in HCT116/3-6 (hMLH1+) cells compared to HCT116 (hMLH1-) cells, we found only modest cytotoxicity (10-20% cell kill) in both cell lines when treated with IdUrd or BrdUrd for 1 population doubling. Upon further anal., the levels of halogenated dThd analogs in DNA were significantly lower (two to three times lower) in HCT116/3-6 cells than in HCT116 cells, and similar results were found in Mlh1+/+ spontaneously immortalized murine embryonic fibroblasts and fibroblasts from Mlh1 knockout mice. As a result of the higher levels of the dThd analog in DNA, there was an increase in radiation sensitivity in HCT116 cells but not in HCT116/3-6 cells after pretreatment with IdUrd or BrdUrd when compared to treatment with radiation alone. Addnl., we found no differences in the cellular metabolic pathways for dThd analog DNA incorporation because the enzyme activities of dThd kinase and thymidylate synthase, as well as the levels of triphosphate pools, were similar in HCT116 and HCT116/3-6 cells.

These data suggest that the hMLH1 protein may participate in the recognition and subsequent removal of halogenated dThd analogs from DNA. Consequently, whereas MMR-deficient cells and tumor xenografts have shown intrinsic resistance to a large no. of chemotherapeutic agents, the 5-halogenated dThd analogs appear to selectively target such cells for potential enhanced radiation sensitivity.

Answer 2:

Bibliographic Information

Antitumor efficacy of seventeen anticancer drugs in human breast cancer xenograft (MX-1) transplanted in nude mice. Inoue, Katsuhiro; Fujimoto, Shuichi; Ogawa, Makoto. Div. Clin. Chemother., Cancer Chemother. Cent., Tokyo, Japan. Cancer Chemotherapy and Pharmacology (1983), 10(3), 182-6. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 99:98704 AN 1983:498704 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activity of 17 anticancer drugs was studied in the treatment of a human breast cancer tumor (MX-1) transplanted into nude mice. The antitumor activity of the drugs was evaluated at the LD10 predetd. in mice as a std. therapeutic dose. Drugs were administered i.v., i.p., or orally, and antitumor activity was assessed by drug-induced growth inhibition measured by calipers. Among the 17 anticancer drugs, the most active compds. (max. inhibition of rate of tumor growth: ≥90%) are mitomycin C, chromomycin A3, vincristine, vinblastine, vindesine, and hexamethylmelamine. Another group of compds. showed moderate activity (max. inhibition rate of tumor growth: 89%-50%), these being adriamycin, daunomycin, mitoxantrone, bleomycin, 5-fluorouracil, 6-thioguanine, and ftorafur.

The remaining 4 drugs (peplomycin, cytosine arabinoside, 6-mercaptopurine, and methotrexate) were inactive against the MX-1 tumor. These results suggest that in the nude mouse-human tumor xenograft system there is a good correlation between the antitumor activity of various anticancer drugs and their clin. efficacy; this system is therefore expected to be a useful model for secondary screening.

Answer 3:

Bibliographic Information

Chemotherapy of cell-line-derived human colon carcinomas in mice immunosuppressed with antithymocyte serum. Tibbetts, Lance M.; Chu, Ming Y.; Hager, Jean C.; Dexter, Daniel L.; Calabresi, Paul. Dep. Med., Brown Univ., Providence, RI, USA. Cancer (New York, NY, United States) (1977), 40(5, Suppl.), 2651-9. CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 88:115007 AN 1978:115007 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

An in vivo model is described for assessing the antitumor activity of chemotherapeutic agents. Tumors derived from human colon carcinoma cell lines injected into antithymocyte serum (ATS) immunosuppressed mice were used. In this system, both antitumor effects and host toxicity can be quantitated, permitting calcn. of a therapeutic Index. Compared with other xenograft models, the present system is simple. Expts. are completed in less than 2 wk, and the use of cultured cell lines allows in vitro studies to be performed. The in vitro sensitivities of 1 colon cell line to 22 chemotherapeutic agents and of 4 cell lines to 3 agents is reported. Four drugs used in treating colon cancer (mitomycin C [50-07-7], 5-fluorouracil [51-21-8], BCNU [154-93-8], methyl-CCNU [13909-09-6]) showed antitumor activity in vivo in this system. Each had a low therapeutic index.

Answer 4:

Bibliographic Information

Inhibitory effect of 8-oxo-7,8-dihydro-2'-deoxyguanosine on the growth of KG-1 myelosarcoma in Balb/c nude mice. Choi Seongwon; Choi Hyun Ho; Choi Jun-Ho; Yoon Byung-Hak; You Ho Jin; Hyun Jin-Won; Kim Ja-Eun; Ye Sang-Kyu; Chung Myung-Hee Department of Pharmacology, College of Medicine, Seoul National University, Seoul, Republic of Korea Leukemia research (2006), 30(11), 1425-36. Journal code: 7706787. ISSN:0145-2126. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16678259 AN 2006528773 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We previously found that 8-oxo-7,8-dihydro-2'-deoxyguanosine (oh(8)dG) kills KG-1, a human myelocytic leukemic cell line with mutational loss of 8-oxoguanine glycosylase (OGG1) activity in vitro. This observation prompted us to investigate the cytotoxicity of oh(8)dG on KG-1 in vivo. This cytotoxicity was observed by administrating oh(8)dG (3.3-330mg/kgb.w./day) for 14 days into nude mice bearing a KG-1 myelosarcoma. The results were as follows; oh(8)dG inhibited the growth of KG-1 myelosarcoma dose-dependently in terms of tumor size and weight, but had no effect on the growth of myelosarcoma of U937, a human monocytic leukemic cell line possessing wild-type OGG1. 6-Thioguanine (6-TG), an anticancer drug inhibited the growths of KG-1 and U937 tumors. 2'-Deoxyguanosine (dG) had a statistically insignificant anti-growth effect on both tumors. The oh(8)dG-treated KG-1 tumor showed the increased expression of apoptosis-processing caspases 8, 9 and 3 together with DNA fragmentation, the increased expression of cell cycle inhibitors, p16 and p27, and the decreased expression of cell cycle accelerator, cyclins and cdks, indicating the nature of cytotoxicity is cell cycle arrest and apoptosis. The genomic DNA of oh(8)dG-treated KG-1 tumors showed an increase in OGG1 sensitive sites, which is consistent with an increase in the 8-oxo-7,8-dihydroguanine (oh(8)Gua) level in the DNA of KG-1 treated with oh(8)dG in vitro. Presumably an increased level of oh(8)Gua in DNA may trigger the cytotoxicity. These findings suggest that oh(8)dG is selectively cytotoxic to KG-1 or tumors that are OGG1-deficient.

Answer 5:

Bibliographic Information

Guanosine nucleotides inhibit different syndromes of PTHrP excess caused by human cancers in vivo. Comment in: J Clin Invest. 2002 Nov;110(10):1399-401. PubMed ID: 12438435 Gallwitz Wolfgang E; Guise Theresa A; Mundy Gregory R OsteoScreen Ltd., San Antonio, Texas 78229, USA. gallwitz@osteoscreen.com The Journal of clinical investigation (2002), 110(10), 1559-72. Journal code: 7802877. ISSN:0021-9738. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 12438453 AN 2002678469 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

There are two well-described syndromes caused by tumor production of parathyroid hormone-related peptide (PTHrP), namely osteolytic bone disease associated with breast cancer and humoral hypercalcemia of malignancy (HHM) that occurs with or without bone metastasis. Both syndromes have been shown experimentally to be inhibited by neutralizing antibodies to PTHrP. In a search for small-molecule inhibitors of PTHrP production or effects, we have identified guanine-nucleotide analogs as compounds that inhibit PTHrP expression by human tumor cells associated with these syndromes. We show in nude athymic murine models that these compounds reduce PTHrP-mediated osteolytic lesions associated with metastatic human breast-cancer cells as well as the degree of hypercalcemia caused by excessive PTHrP production by a squamous-cell carcinoma of the lung. These results suggest that the PTHrP gene promoter may be a suitable target for treating the skeletal effects of malignancy.

Answer 6:

Bibliographic Information

Multifaceted resistance of gliomas to temozolomide. Bocangel Dora B; Finkelstein Sydney; Schold S Clifford; Bhakat Kishor K; Mitra Sankar; Kokkinakis Demetrius M Department of Pathology, The University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania 15261, USA Clinical cancer research : an official journal of the American Association for Cancer Research (2002), 8(8), 2725-34. Journal code: 9502500. ISSN:1078-0432. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 12171906 AN 2002417756 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE AND EXPERIMENTAL DESIGN: The contributions of O6-methylguanine-DNA-methyltransferase(MGMT), p53 status, mismatch repair, and apoptotic response to the resistance of glial tumors to temozolomide (TMZ) were tested using seven established human glial tumor cell lines in culture and xenografts in athymic mice. RESULTS: Resistance to TMZ was only marginally dependent on MGMT activity, because subtoxic doses of TMZ easily eliminated MGMT reserves for at least 18 h after treatment. Resistance to TMZ varied most notably with the p53 status of the tumor. Tumors with wild-type (wt) p53 and a functional p53 response to DNA damage (SWB40 and SWB61) were most sensitive. The p21-related cell cycle arrest was intimately linked to TMZ toxicity because tumors with wt p53 but lacking a robust increase in p21 protein level (D-54) were resistant to TMZ. In contrast, tumors with a dysfunctional p53 cycle and a weak cell cycle response to DNA damage (SWB39 and SWB77) were extremely unresponsive to treatment even with the aid of MGMT inactivators. Notable exceptions to the above were observed with the p53 mutated tumors SWB33 and SWB95, which were arrested by TMZ in G1-S and consequently underwent apoptosis despite their failure to express p21. CONCLUSIONS: By testing a limited number of glial tumors in cell culture and also as xenografts, we have shown that mobilization of the p53 in response to TMZ damage is likely to induce a cell cycle arrest and apoptosis in glial tumors. Additional pathways linking cell cycle arrest and apoptosis contribute to the efficacy of TMZ against p53 mutated glial tumors. The unusual resistance of tumors, of which the cell cycle was not arrested in response to TMZ treatment, was associated with allelic losses during regrowth of treated tumors. Nevertheless such resistance was not related to dysfunctional mismatch repair.

Answer 7:

Bibliographic Information

Escherichia coli gpt gene sensitizes rat glioma cells to killing by 6-thioxanthine or 6-thioguanine. Tamiya T; Ono Y; Wei M X; Mroz P J; Moolten F L; Chiocca E A Department of Surgery, Massachusetts General Hospital, Boston 02129, USA Cancer gene therapy (1996), 3(3), 155-62. Journal code: 9432230. ISSN:0929-1903. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 8725879 AN 96348743 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Genes that encode enzymes that convert inactive "prodrugs" into anticancer metabolites may be therapeutically useful against brain tumors. Unlike other genes tested to date in brain tumor models, the Escherichia coli gpt gene is unique in that it not only sensitizes cells to the prodrug 6-thioxanthine (6TX) but also encodes resistance to a different regimen (mycophenolic acid, xanthine, and hypoxanthine), thus providing a means to select for gpt-positive cells. In the present study, rat C6 glioma cells were infected with a retrovirus vector that transduces this gene. A clonal line (C6GPT-7) was derived that exhibited significant 6TX susceptibility in vitro with an ID50 of 2.5 mumol/L, whereas 50% growth inhibition of parental C6 cells was not achieved at concentrations tested (up to 50 mumol/L). This line also exhibited significant sensitivity to 6-thioguanine (6TG), with an ID50 of 0.05 mumol/L, whereas 50% growth inhibition of parental C6 cells was achieved at 0.5 mumol/L. In a "bystander" assay, C6GPT-7 tumor cells efficiently transferred 6TX sensitivity to C6 cells at ratios as low as 1:9 (C6GPT-7:C6). This in vitro bystander effect was abrogated when C6GPT-7 and C6 cells were separated by a microporous membrane, suggesting that it was not mediated by highly diffusible metabolites. In vivo both 6TX and 6TG significantly inhibited the growth of subcutaneously transplanted C6GPT-7 cells but not that of C6 cells in athymic mice. In an intracerebral model, both 6TX and 6TG exhibited significant antiproliferative effects against tumors formed by C6GPT-7 cells. These findings provide a basis for exploring further gene therapy strategies based on in vivo transfer of the E coli gpt gene to provide chemosensitivity against 6TX and 6TG.

Answer 8:

Bibliographic Information

Positive therapeutic interaction between thiopurines and alkylating drugs in human glioma xenografts. Wang A M; Elion G B; Friedman H S; Bodell W J; Bigner D D; Schold S C Jr Duke University Medical Center, Durham, NC 27710 Cancer chemotherapy and pharmacology (1991), 27(4), 278-84. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 1998983 AN 91152817 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We used human anaplastic glioma xenografts to evaluate the therapeutic efficacy of combinations of alkylating drugs, either 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-(2,5-dioxo-3-piperidyl)-1-nitrosourea (PCNU), or procarbazine, and thiopurines, either 6-mercaptopurine (6MP) or 6-thioguanine (6TG). Using growth delay as the endpoint in subcutaneous (s.c.) tumors and increased life span as the endpoint in intracranial (i.c.) tumors, we found that combinations of chloroethylnitrosoureas (CENUs) and thiopurines were significantly more active than either type of agent alone. In contrast, combinations of procarbazine and thiopurines were not significantly more active than procarbazine alone. The therapeutic potentiation of the CENU was greater when the latter was given on the 4th day of the thiopurine treatment cycle than when it was given on the 1st day. Characterization of the interaction between CENUs and thiopurines also revealed a supraadditive therapeutic response at higher BCNU doses in combination with 6TG. Interaction between the nitrosoureas and the thiopurines probably occurs in the guanine base of tumor DNA and has important therapeutic implications.